Success evaluation of Assisted Reproductive Technology in couples with chromosomal abnormalities

Ana Rita Jesus[1], Sandra Silva-Soares[2], Joaquina Silva[3], Milton Severo[4,5], Alberto Barros[1,3,6], Sofia Dória[1,6]

1= Genetics Department, Faculty of Medicine, University of Porto (FMUP), 2= Unidade de Medicina da Reprodução, Centro Hospitalar Universitário São João (CHUSJ),
3= Centro de Genética e Reprodução Professor Alberto Barros,
4= EPIUnit - Institute of Public Health, University of Porto, Department of Public Health and Forensic Sciences and Medical Education, Faculty of Medicine, University of Porto (FMUP),
6=I3S – Instituto de Investigação e Inovação em Saúde, University of Porto

Corresponding author:
e-mail address: sdoria@med.up.pt
address: Genetics Department, Faculty of Medicine, Alameda Professor Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL
telephone number: 00351914641924

Information about the authors:
Ana Rita Jesus - Address: Professor Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL; ORCID: 0000-0002-2649-5430
Sandra Silva-Soares - Address: Professor Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL
Joaquina Silva - Address: Avenida do Bessa, 4100-012 Porto, PORTUGAL
Milton severo- Address: Professor Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL; ORCID: 0000-0002-5787-4871
Alberto Barros- Address: Avenida do Bessa, 4100-012 Porto, PORTUGAL; ORCID: 0000-0002-8700-3698
Sofia Dória- Address: Professor Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL; ORCID: 0000-0001-9225-9076

Acknowledgments
We acknowledge Centro de Genética e Reprodução Professor Alberto Barros's team and Mrs Susana Coutinho from Centro Hospitalar Universitário São João for their support in data gathering.

Success evaluation of Assisted Reproductive Technology in couples with chromosomal abnormalities

Abstract

Purpose: Infertility is estimated to affect 15% of couples, and chromosome abnormalities play an important role in its etiology. The main objective of this work is to access the reproductive success of ART in infertile couples with chromosomal abnormalities comparing to a control group with normal karyotype.

Methods: A retrospective analysis of seven years of all karyotypes performed in couples with infertility was done. Data regarding type of infertility, couples' ages, ART performed and their reproductive success were obtained from medical records. Adjusted Odds Ratio (OR) were used to estimate magnitude of association between the success and the different exposures/groups.

Results: We found a prevalence of 7.83% (234/2989) of chromosome abnormalities in our population. Chromosomal anomalies were found in 83 men (35.02%) and 154 women (64.98%), with low-grade mosaicism being the most prevalent (50.63%), followed by autosomal translocations (17.30%) and sex chromosomes abnormalities (13.92%). There was a non-significant lower success rate in the cases, OR=0.899, p=0.530), with IVF treatment providing the higher success rate. Secondary infertility was significant for lower probability of success (OR=0.643, p<0.001). In general female carriers of chromosome anomalies had a higher success rate, although not significant.

Conclusion: Although the differences regarding success rate between groups were not found statistically significant, we still advocate that cytogenetic analysis should be performed routinely in all infertile couples namely before ART. This might help deciding the best treatment options including Preimplantation Genetic Test for aneuploidies or structural rearrangements and minimize the risk of transmission of anomalies to the offspring.

Keywords

Infertility, chromosome abnormalities, Assisted Reproduction Technology, karyotype.

Introduction

Infertility is defined by the World Health Organization (WHO) and by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) as a disease of the reproductive system in which there is failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Infertility is of high prevalence around the world, especially among developing countries, being estimated that 1 out of 4 couples are infertile [2], a tendency that appears to be increasing [2, 3]. Among the several causes of human infertility, genetic abnormalities take an important part [4], with some estimates pointing to being the main factor in up to 50% of infertility cases [5]. Despite the difficulty in studying the genetic implications on fertility, some specific genetic anomalies have been associated with this problem, among which several chromosomal abnormalities [4], that may affect only one or both couple's members.

In this context, an increasing amount of couples has turned to Assisted Reproductive Technology (ART) to find an answer to their reproductive needs [6], using techniques such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI) [7]. This includes those couples that present chromosomal abnormalities as well. However, there are not many studies regarding the success of these techniques in carriers of a chromosome anomaly, especially considering both the female and the male contribution, and the impact of those anomalies in the outcome. Furthermore, such studies usually use small series which make it difficult to draw definite conclusions.

In this context, we aimed to assess the reproductive success of ART in infertile couples with chromosomal abnormalities comparing to a control group also submitted to ART but with normal karyotype.

Methods

A retrospective cohort of all karyotypes performed in the Genetics Department of Faculty of Medicine, University of Porto (FMUP) with the clinical indication of infertility, was done. For this study, a 7 years period was considered, from January 2010 to February 2017. The Ethics Committee for Health of Centro Hospitalar Universitário São João (CHUSJ) approved this study.

To perform the karyotypes, cell culture and standard cytogenetic methods were used. Preparation of chromosome slides and high resolution G banding using Leishman stain were performed according to standard protocols [8]. At least 20 metaphases were counted, all performed according to the Laboratory protocol for karyotype analysis [8]. The International System for Human Cytogenetic Nomenclature (ISCN) was followed for defining the chromosomal aberrations. Information regarding type and prevalence of chromosomal abnormalities was recorded.

Data regarding type of infertility, couples' ages, ART techniques performed and success of those techniques were obtained afterwards from paper registers at a tertiary hospital (Centro Hospitalar Universitário São João - CHUSJ) and from the electronic medical database of a private ART center. We excluded from comparison all couples that did not engage in any ART technique, either for choice or for any medical reasons (e.g. due to advanced maternal age or spontaneous pregnancy).

Infertility was classified into primary and secondary. Primary infertility was defined as inability to become pregnant or the inability to carry a pregnancy to a live birth, whereas secondary infertility was defined as inability to become pregnant or the inability to carry a pregnancy to a live birth after a previous pregnancy, according to the definition by the WHO [2]. Ovulation induction (OI), In Vitro Fertilization (IVF), Intra Cytoplasmic Sperm Injection (ICSI), Intrauterine Insemination (IUI), and Frozen or Vitrified Embryo Transfer (FET), performed either with material from the infertile individual or from a donor, were the techniques performed in both reproductive centers. FET was considered as an independent technique to differentiate multiple transfers of embryos resulting from a previous technique.

To conduct a comparative analysis, two groups were established attending the presence or absence of chromosomal abnormalities (cases and controls). Success was defined as pregnancy with delivery of a healthy baby (*take home baby*). The statistical analysis of the data was performed using the program IBM SPSS Statistics 25. Chi-square test and exact Fisher test were performed for proportions comparison between groups. Adjusted Odds Ratio (OR) were used to estimate magnitude of association between the success and the different groups. Conditional logistic regression was used to estimate the Odd Ratio (OR) and the respective 95% Confidence intervals. Statistical significance level was established at 0,05.

Results

From a seven years period, 2989 couples were tested for chromosomal anomalies as standard evaluation for infertility study in the Genetics Department of Faculty of Medicine of Porto. Chromosomal abnormalities were identified in 234 couples, accounting for 7.83% (234/2989) of total. Type and frequency of such anomalies are listed on table 1. Both members were affected in 3 couples, accounting for a total of 237 (3.96%) individuals with abnormal karyotype. Chromosomal anomalies were found in 83 men (83/237, 35.02%) and 154 women (154/237, 64.98%). Low grade mosaicism was the most prevalent anomaly, affecting 50.63% of individuals, followed by autosomal translocations (17.30%) and sex chromosomes abnormalities (13.92%). It should be noted that the type of anomaly varied between genders. Sex chromosome abnormalities were more prevalent in the male partner (33.73% of males vs. 3.25% of females). Klinefelter syndrome was the most common sex chromosome abnormality, being found in 19/83 (22.89%) of males. Mosaicism, on the other hand, was much more prevalent among women that men (67.53% of females vs. 19.28% of males). Mosaic Turner syndrome was found in 92/154 women (59.74%), accounting for the large majority. Autosomal structural abnormalities were found in 32.49% individuals (77/237), the most frequent being translocations (62/77, 80.52%), in both genders.

Only 2359 couples proceeded with an ART technique, which included 162 cases and 2197 controls. Mean age was 38.87 years for women and 40.41 for men. Information regarding the type of infertility and success rate is summarized on table 2 for both groups. A vast majority of 80.12% of couples haven't had a previous pregnancy or have had a miscarriage before. We found a 49.55% success rate for all couples.

Number of procedures to success is summarized on table 3. A majority of 68.16% of couples engaged in only 1 procedure. On average, 2.21 fertility treatments (median = 2.00) were necessary to achieve a successful outcome. Number of newborns for pregnancy is also summarized on table 3. An average of 1.10 babies were born for each pregnancy. Miscarriages accounted for 12.46% of all pregnancies.

Type and frequency of the last procedure performed is shown on table 4. ICSI was by far the most frequent, being the last technique offered to 50.74% of all couples. On the other hand, IO and treatment using donor gametes were much less frequent, accounting for only 2.67% and 0.72% of couples, respectively.

Table 5 presents the association between success and multiple variables considered in this study. There was a slightly lesser rate of success in the cases group, although not statistically significant (OR=0.899, p=0.530). IVF was significantly superior to the other ART techniques, with exception of procedures performed with donor gametes, that was associated with a non significant higher rate of success (OR=1.194, p=0.738). A probability of success was negatively associated with increasing age of female partner (OR=0.937, p<0.001). Secondary infertility

was negatively associated with the probability of success (OR=0.643, p<0.001). An association between higher number of procedures and small rate of success was found, although not significant (OR=0.970, p=0.306).

Rate of success outcome according to type of anomaly and gender of the member affected is summarized on Figure 1. There is a higher rate of success when the female is the carrier, with exception of sex chromosome anomalies. However this differences were not significant (p=0.810, for inversions; p=0.314, for translocations; p=0.232, for mosaics). A great disparity between genders regarding success was found in inversion's carriers, with all couples in which the female was the carrier having an 100% success rate (versus 37.5% for couples with male carriers).

Discussion

Infertility is a condition of increasing prevalence [2, 3] that has a multifactorial cause and therefore a complex treatment [9]. Comprehensive study of both members of the couple is essential to maximize the probability of pregnancy and minimize the transmission of genetic anomalies to the offspring. Chromosome abnormalities seem to play an important role in the etiology of infertility[4], making karyotype testing an useful tool to understand chromosomal anomalies and their impact on human reproduction. In this study, as part of the routine evaluation of the infertile couple, karyotype testing allowed the identification of previously undiagnosed chromosome abnormalities in 234 couples, which accounts for 7,83 % (234/2.989) of our population. This is consistent with recent studies [10-12] that reported a similar prevalence of chromosomal anomalies in the infertile population, a rate 2-3 times higher than the general population [13].

All individuals were evaluated by the same laboratory, which leave virtually no space for differences in interpretation of cytogenetic results. However, information regarding age, type of infertility, ART procedures performed and outcome were collected from two different fertility centers, from paper and electronic registers. Some information bias may therefore distort these results. Diagnostic methods, techniques' protocols and success rates may also vary between centers. Nevertheless, no statistical differences were found comparing the successful outcome of both centers.

Chromosomal abnormalities were more frequent among women than men (64,98% vs. 35,02%). This seems to disagree with others studies that reported higher frequency of abnormal karyotype in men than women [11], while others report an 1:1 ratio [14]. These differences may be due to regional disparities, different inclusion criteria for the study population and type of anomaly considered. Low grade mosaicism, which is often excluded from analysis, was included in our study and may explain these differences. Mosaics were by far the most prevalent anomaly, accounting for 50,63% of affected individuals, and was mainly found in women, mosaic monosomy X being the most common. This represents an important cause of infertility, considering that primary amenorrhea and lack of pubertal development presents in 90% of women with 45,X or with 45,X mosaicism with 46,XY, 46,XX or 47,XXX [15], and is consistent with findings from similar studies [12]. Because it has been shown that the frequency of low-level X aneuploidy is correlated with age and gender but not with reproductive history [16], we conducted the same analysis performed in table 5 for all couples but removing all the mosaic cases. The results obtained were not statistical different from those showed in table 5, so we chose to keep all couples in the analysis.

Sex chromosome abnormalities were more frequent among infertile men, the most common being Klinefelter syndrome. Other studies have reported similar results [10, 12, 17]. The most common pericentric inversion of the Y chromosome, 46,X,inv(Y)(p11q11), was found in 5 men.

For a long period of time, this chromosomal polymorphic variation was considered a normal variation but some recent studies have reported an association with poor spermatogenesis and production of unbalanced gametes [13, 18], although there is still controversy regarding this subject.

Autosomal translocations were the second most common anomaly found in our study population, followed by sex chromosome anomalies and inversions. Balanced translocations and other autosomal abnormalities may have an impact in the fertility of an otherwise phenotypically normal individual, due to the production of unbalanced gametes with abnormal chromosome pairing and segregation at meiosis I [19, 20]. This increases the risk of miscarriage and birth of a child with abnormal karyotype [21].

A significant number of infertile couples decided not to initiate treatment or engage in any further ART procedure. This is demonstrative of the enormous financial burden and psychological exhaustion that infertile individuals are exposed [22]. Only 2.359 couples, 162 of which had at least one member affected by a chromosome abnormality, proceeded to ART. Mean age for these couples was 38,87 years for women and 40,41 for men, which reflect the current tendency among developing countries of postponing maternity [23, 24].

Pregnancies resulted in 1,1 newborns, on average. The success rate of the overall population was 49,55%, which is similar to rates reported by other studies [20, 25]. Successful outcome was achieved after a medium of 2,21 fertility treatments, with a majority of couples receiving only 1 procedure. This may be explained by high success rates on the first technique, financial inability to proceed to another treatment or psychological distress after a first failed attempt. An average of 1,10 babies were born for each pregnancy. Miscarriages accounted for 12,46% of all pregnancies.

When analyzing the last procedure performed, ICSI was by far the most frequent. This is not surprising since ICSI is a much more exigent technique. On the contrary, IO is usually more used as a first approach procedure, being less technically exigent, less time and money consuming and less invasive. Procedures using donor gametes are viewed as an end of the line treatment, and as such weren't performed frequently. We have to keep in mind that ART is not assigned randomly by the doctor, but chosen according to the characteristics of each individual, in order to maximize the chances of a successful outcome. Thus, karyotype results were considered when deciding which treatment to offer, and this may explain why procedures using donor gametes were more commonly used among cases than controls.

Success rate was higher in the control group, although this was not statistically significant. As chromosome abnormalities are a known cause of infertility, some differences regarding success rate might be expected between groups. However, studies reporting success rates of ICSI among couples with chromosomal abnormalities also found no significant differences from a control group [26, 27]. This might be explained by the fact that ovarian stimulation, required

to perform any ART technique, may extend the process of natural selection thus increasing the rejection of abnormal oocytes and the probability of producing a normal embryo [28]. In addition to this, infertility is a multifactorial complex pathology, and other relevant aspects may distort these results. As mention previously, treatments were not randomly assigned to couples, but chosen according to its characteristics, chromosome anomalies included, which may also contribute to a higher success rate among the cases and an attenuation of differences between groups. Techniques using donor gametes were more commonly performed in the cases, which is an alternative that bypasses the genetic anomalies and may also mitigate any differences regarding success. In addition to this, it was considered inappropriate to initiate treatment in some couples with major chromosome abnormalities, which may further attenuate any possible differences between groups.

A significant lesser probability of success was associated with increasing age of female partner. Decreasing fertility with age is already a well established relationship [29-31].

We found that IVF treatments were significantly superior to the other ART with the exception of techniques performed with donor gametes. As mention before, donor treatments bypass the possible anomalies present in the couple, making unsurprising that they offer better results.

Secondary infertility was significant for lower probability of success. At first sight, this may seem contra-intuitive. However, couples that present secondary infertility are often of older age, a factor already established as an important factor in decreasing fertility. Other important factors may be involved in the loss of fertility, including endocrine, metabolic, urologic and gynecologic pathologies that may require other type of treatments and further decrease the probability of success. An association between higher number of procedures and small rate of success was found, although not significant. An explanation for this is the fact that this couples present with an unknown infertility cause that is so severe that no matter the number of treatments performed, success will never be achieved.

Taking into account success according to type of chromosome anomaly, it is clear in figure 1 that the outcome was better when the carrier of a translocation, inversion or even a mosaic was a woman. This could be explained by the fact that gametogenesis in the male is more vulnerable to the stumbling block imposed by a chromosomal abnormality. According to literature, another important element is the impaired synapsis of homologous segments in the normal and the rearranged chromosomes, which itself could prevent further progress in gametogenesis. Spermatogenesis may be more sensitive to this obstacle than oogenesis [32-34].

In the case of a non-mosaic sexual chromosomal abnormality either structural or numerical, a success outcome was achieved in about 50 % of cases with affected male individuals. This rate could be explained, at least partially, by the development of ICSI and testicular sperm extraction that could be applied to Klinefelter patients, allowing the possibility of fathering to be

a reality for these individuals .A previous study from our group also concluded that there is no increased risk for aneuploidies in the offspring [35]. Regarding women with non-mosaic sexual chromosomal abnormality, only 5 cases were included and so no conclusion could be made.

Finally, some authors have argued that ART techniques, such as ICSI, may contribute to the propagation of chromosome abnormalities to the offspring, even when parents are not affected by any anomaly [36]. Studies are beginning to report on genetic and epigenetic impact of such techniques, with some reporting an increased risk of multiple pathologies [37, 38]. This furthers enhances the need for karyotype testing before engaging in any procedure. Reproductive counseling including the option of Preimplantation Genetic Test for aneuploidies (PGT-A) or structural rearrangements (PGT-SR) should be given to the infertile couple to minimize the risk of transmission of anomalies to the offspring.

Conclusion

Chromosome abnormalities are an important cause of infertility, being found in a significant percentage of the infertile population. Although the differences regarding success rate between cases and controls were not found statistically significant, we still advocate that cytogenetic analysis should be performed routinely in all infertile men and women due to the fact that it might help deciding the best fertility treatment options to offer the couple. Furthermore, there are still questions regarding the risk of transmission of anomalies to the offspring and the impact of such anomalies in the future child. Genetic counseling and PGT-A/PGT-SR should therefore be offered to couples in this situation. Infertility is a very complex issue that is far from being completely understood. It is clear that more evidence is needed in order to make any definite conclusion about the impact of chromosome abnormalities on human infertility and usefulness of ART techniques in these individuals.

Keywords

Infertility, chromosome abnormalities, Assisted Reproduction Techniques,

Acknowledgments

We acknowledge Centro de Genética e Reprodução Professor Alberto Barros's team and Mrs Susana Coutinho from Centro Hospitalar Universitário São João for their support in data gathering.

References

1. *Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertility and sterility. 2009;92(5):1520-4.*
2. *Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS medicine. 2012;9(12):e1001356.*
3. *Soini S, Ibarreta D, Anastasiadou V, Ayme S, Braga S, Cornel M, et al. The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. European journal of human genetics : EJHG. 2006;14(5):588-645.*
4. *Shah K, Sivapalan G, Gibbons N, Tempest H, Griffin DK. The genetic basis of infertility. Reproduction (Cambridge, England). 2003;126(1):13-25.*
5. *Zorrilla M, Yatsenko AN. The Genetics of Infertility: Current Status of the Field. Current genetic medicine reports. 2013;1(4).*
6. *Butler P KJ. Assisted reproduction in developing countries-facing up to the issues. Prog Hum Reprod Res. 2003;63:1-8.*
7. *Okhovati M, Zare M, Zare F, Bazrafshan MS, Bazrafshan A. Trends in Global Assisted Reproductive Technologies Research: a Scientometrics study. Electronic Physician. 2015;7(8):1597-601.*
8. *Madureira CB MM, Alves C, Pereira S, Lemos MF, Reis MF, Dória S, Sousa M, Barros A. Técnicas de bandeamento cromossómico em citogenética. Caso de um paciente masculino com infertilidade conjugal e cromossoma supranumerário no cariótipo do sangue periférico. Micron 2005. 2004;12:20-7.*
9. *Izzo CR, Monteleone PA, Serafini PC. Human reproduction: current status. Revista da Associacao Medica Brasileira (1992). 2015;61(6):557-9.*
10. *Olesen IA, Andersson AM, Aksglaede L, Skakkebaek NE, Rajpert-de Meyts E, Joergensen N, et al. Clinical, genetic, biochemical, and testicular biopsy findings among 1,213 men evaluated for infertility. Fertility and sterility. 2017;107(1):74-82.e7.*
11. *Demirhan O TN, Süleymanova D. Chromosomal Aberrations in Turkish Infertile Couples with Reproductive Problems. Glob J Fertil Res. 2016;1(1):006-10.*
12. *Mierla D, Malageanu M, Tulin R, Albu D. Prevalence of chromosomal abnormalities in infertile couples in romania. Balkan Journal of Medical Genetics : BJMG. 2015;18(1):23-30.*
13. *Kate UV, Pokale YS, Jadhav AM, Gangane SD. Chromosomal Aberrations and Polymorphic Evaluation in Males with Primary Infertility from Indian Population. Journal of Clinical and Diagnostic Research : JCDR. 2014;8(10):Sc01-6.*
14. *Bohiltea LCR, Viorica; Bohiltea, Roxana. Genetic Causes of Infertility: Chromosomal Abnormalities in Couples with Reproductive Failure. Ginecoro. 2009;5(2):106-11.*
15. *Folsom LJ, Fuqua JS. Reproductive Issues in Women with Turner Syndrome. Endocrinology and metabolism clinics of North America. 2015;44(4):723-37.*
16. *Madan K, Lundberg E S. Low grade mosaicism for X aneuploidy in women referred for recurrent abortions: European Cytogeneticists Association Newsletter; 2015. 9-12 p.*
17. *Mascarenhas M, Thomas S, Kamath MS, Ramalingam R, Kongari AM, Yuvarani S, et al. Prevalence of chromosomal abnormalities and Y chromosome microdeletion among men with severe semen abnormalities and its correlation with successful sperm retrieval. Journal of human reproductive sciences. 2016;9(3):187-93.*
18. *Sahin FI, Yilmaz Z, Yuregir OO, Bulakbasi T, Ozer O, Zeyneloglu HB. Chromosome heteromorphisms: an impact on infertility. Journal of assisted reproduction and genetics. 2008;25(5):191-5.*
19. *Zhang YP, Xu JZ, Yin M, Chen MF, Ren DL. [Pregnancy outcomes of 194 couples with balanced translocations]. Zhonghua fu chan ke za zhi. 2006;41(9):592-6.*
20. *Idowu D, Merrion K, Wemmer N, Mash JG, Pettersen B, Kijacic D, et al. Pregnancy outcomes following 24-chromosome preimplantation genetic diagnosis in couples with balanced reciprocal or Robertsonian translocations. Fertility and sterility. 2015;103(4):1037-42.*
21. *Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Human reproduction (Oxford, England). 2006;21(4):1076-82.*
22. *Hasanpoor-Azghdy SB, Simbar M, Vedadhir A. The emotional-psychological consequences of infertility among infertile women seeking treatment: Results of a qualitative study. Iranian Journal of Reproductive Medicine. 2014;12(2):131-8.*
23. *Waldenström U. Postponing parenthood to advanced age. Upsala journal of medical sciences. 2016;121(4):1-9.*

24. Mills M, Rindfuss RR, McDonald P, te Velde E, Reproduction E, Society Task F. Why do people postpone parenthood? Reasons and social policy incentives. Human reproduction update. 2011;17(6):848-60.
25. Guo KMW, B.; Wang, H.B.; Tian, R.H. . Reproductive outcome of male carriers of chromosomal abnormalities: multidisciplinary approach for genetic counseling and its implications. Genet Mol Res 2016; 15 (4):gmr15048963.
26. Yin B, Zhu Y, Wu T, Shen S, Zeng Y, Liang D. Clinical outcomes for couples containing a reciprocal chromosome translocation carrier without preimplantation genetic diagnosis. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2017;136(3):304-8.
27. Maiburg M, Alizadeh B, Kastrop P, Lock M, Lans S, Giltay J. Does the genetic and familial background of males undertaking ICSI affect the outcome? Journal of assisted reproduction and genetics. 2009;26(6):297-303.
28. Menezo Y, Chouteau J, Veiga A. In vitro fertilization and blastocyst transfer for carriers of chromosomal translocation. European journal of obstetrics, gynecology, and reproductive biology. 2001;96(2):193-5.
29. Lourdel E, Merviel P, Cabry-Goubet R, Brzakowski M. [Declining fertility with age]. La Revue du praticien. 2010;60(6):814-9.
30. Speroff L. The effect of aging on fertility. Current opinion in obstetrics & gynecology. 1994;6(2):115-20.
31. Pal L, Santoro N. Age-related decline in fertility. Endocrinology and metabolism clinics of North America. 2003;32(3):669-88.
32. R.J. McKinlay Gardner DJA. Gardner and Sutherland's Chromosome Abnormalities and Genetic Counseling (Oxford Monographs on Medical Genetics. Oxford Monographs on Medical Genetics. April 2018;5th Edition(19).
33. D.W. H. Is X-Y recombination necessary for spermatocyte survival during mammalian spermatogenesis? Cytogenet Cell Genet. 1994;65:278–82.
34. Oliver-Bonet M BJ, Sun F, et al. Meiotic studies in two human reciprocal translocations and their association with spermatogenic failure. Human reproduction (Oxford, England). 2005;20:683–8.
35. Madureira C, Cunha M, Sousa M, Neto AP, Pinho MJ, Viana P, et al. Treatment by testicular sperm extraction and intracytoplasmic sperm injection of 65 azoospermic patients with non-mosaic Klinefelter syndrome with birth of 17 healthy children. Andrology. 2014;2(4):623-31.
36. Byler MC, Lebel RR. Risks of reproducing with a genetic disorder. Seminars in reproductive medicine. 2013;31(4):258-66.
37. Jiang Z, Wang Y, Lin J, Xu J, Ding G, Huang H. Genetic and epigenetic risks of assisted reproduction. Best practice & research Clinical obstetrics & gynaecology. 2017;44:90-104.
38. Chen M, Heilbronn LK. The health outcomes of human offspring conceived by assisted reproductive technologies (ART). Journal of developmental origins of health and disease. 2017;8(4):388-402.